UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

July 24, 2018

To: [redacted]

From: [redacted]

Through: [redacted]

Subject: Updated Review of Systemic Toxicity Data for the PMN substance, P-16-0510

Purpose

This memorandum briefly summarizes EPA's assessment of potential risks associated with identified uses of the PMN substance based on the available analog data. Appendix A, which follows this memorandum, provides a more detailed discussion of EPA's risk assessment of P-16-0510.

Conclusion

Based on the available data on systemic toxicity, EPA concluded that risks were not identified for the PMN substance, P-16-0510, for the general population, consumers or workers, under the conditions of use specified in the PMN.

Background

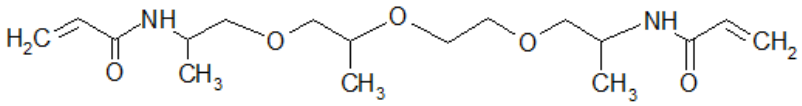
This update is provided at the request of [redacted]. The update includes a review of the calculations used in the original risk assessment and updates for clarity.

At the Structure Activity Team (SAT) meeting on August 19, 2016, the SAT Chair and SAT Health Assessor determined that absorption of the low molecular weight fraction (LMW, 8% < 500, 32% < 1000) of the PMN substance, P-16-0510, is good through the lungs based on physical/chemical properties (estimated water solubility of 1.085 g/L). Poor absorption is expected through the skin and GI tract for the low molecular weight fraction also based on physical/chemical properties. If the PMN Is in solid form, then absorption is predicted to be nil-poor all routes.

P-16-0510 has concern for mutagenicity, developmental toxicity, reproductive effects and neurotoxicity and a marginal concern for oncogenicity based on the acrylamide functional groups. The concerns associated with the PMN substance were communicated to the submitter in an action letter dated March 22, 2017.

Analog Selection

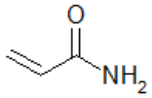
On May 8, 2017, the submitter requested that EPA assess the PMN substance based on a "worst case analog, such as methyl acrylamide". EPA also identified an additional analog, dipropylene glycol diacrylate (DPGD), based on similarity of structure and likely mode of action when compared to the PMN substance. Publicly available, peer reviewed toxicity data were located for both analogs and those data were used to assess potential risks of the PMN substance. EPA assessed risk for the low molecular weight (LMW) fraction of the PMN substance based on read across from the acrylamide data, evaluated in the EPA IRIS 2010 Toxicological Review of Acrylamide (CAS No. 79-06-1), In Support of Summary Information on the Integrated Risk Information System (IRIS), and the ECHA registration data submitted on dipropylene glycol diacrylate (DPGD) and the structural analog 1,6-hexamethylene diacrylate (HDDA) used in this registration (ECHA, 2011). The chemical structures for all of these compounds are provided below.



P-16-0510 CASRN 1792208-65-1

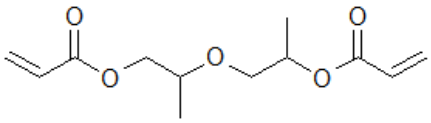
Analogs used to assess health risk

Analog for LMW Fraction of PMN

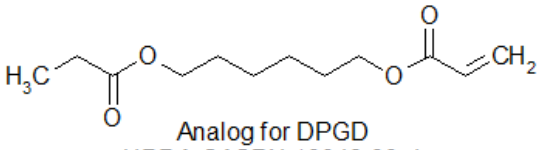


Acrylamide
CASRN 79-06-1

Analog for Entire PMN



DPGD CASRN 57472-68-1



Analog for DPGD
HDDA CASRN 13048-33-4

When considering the relative merits of the analogs, it was noted that both acrylamide and DPGD/HDDA may lead to adverse effects in biological systems *via* Michael Addition reactions; however, acrylamides have been shown to be less reactive than acrylates with cysteine residues (*i.e.*, more than an order of magnitude slower).[1] **Therefore, DPGD/HDDA was selected as the preferred analog for use with determining potential risks of concern for the PMN substance.** The assessment of risks based on acrylamide is included for comparison purposes. A qualitative assessment was performed on the PMN substance for cancer effects (the rationale for this decision is provided in Appendix A). A summary of the outcome of the risk assessment is provided below with the details presented in Appendix A.

Risk Assessment

Hazard Identification and Points of Departure

The ECHA dossier identified a number of systemic effects associated with DPGD/HDDA, including decreased body weight, liver effects (vacuolization and increased liver weights) and clinical chemistry changes (ECHA, 2011). The POD for DPGD/HDDA is based on the NOAEL for systemic effects. Adjustments were made for study duration, body weight, breathing rate, and allometric scaling, as appropriate (refer to Table 1 in Appendix A for details).

The assessment of risk for acrylamide was based on neurotoxicity, the most sensitive endpoint identified in the IRIS assessment (U.S. EPA, 2010). The point of departure (POD) for acrylamide is based on benchmark dose modeling, specifically the benchmark response of 5% extra risk from the EPA IRIS assessment (U.S. EPA, 2010).

[1] Mather *et al*. (2006) *Michael Addition Reactions in Design for Emerging Technologies*, *Macromolecular* PROGRESS IN POLYMER SCIENCE, Vol. 31, pp. 487-531, at p. 523.

Risk Calculation
EPA estimated risks based on the Margin of Exposure (MOE) approach. The calculations are presented in Appendix A. In summary, the risks assessment based on the preferred analog DPGD/HHDA indicates:

- Risks were not identified for the general population for health effects via consumption of drinking water, based on analog data (Table 2).
- Risks were not identified for consumers for health effects via inhalation and dermal contact, based on analog data (Table 3).
- Risks were not identified for workers for health effects via inhalation (Table 4) or dermal exposure (Table 5).

In addition, EPA performed a qualitative assessment of cancer risks taking into account available data, as well as the predicted reactivity based on chemical structures. EPA concluded that a qualitative evaluation of potential cancer risks of concern was sufficient to designate this hazard as a low priority and to determine that quantitative data represented a data gap, but they were not needed on this endpoint to quantify potential risk(s).

Conclusions
EPA concludes that the non-cancer and cancer risks are adequately mitigated under the scenarios evaluated.

Uncertainties
Absorption is based on physical chemical properties.
There is limited information on the PMN substance itself; risks were evaluated based on analog data.

There is uncertainty regarding selection of the analogs for risk assessment. However, EPA selected the most appropriate analog for risk assessment after considering the relative reactivity and mode of action of two well studied analogs.

Potentially Useful Information
Potentially useful information would inform understanding of absorption, specific target organ toxicity, reproductive and developmental toxicity and neurotoxicity.

References
ECHA (2011) *Oxybis(methyl-2,1-ethanediyl) diacrylate, EC number: 260-754-3, CAS number: 57472-68-1*, European Chemicals Agency (ECHA), available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14685/1

EPA (2010) *Toxicological Review of Acrylamide (CAS No. 79-06-1), In Support of Summary Information on the Integrated Risk Information System (IRIS)*, EPA/635/R-07/009F, 459 pp., available at: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0286tr.pdf

Appendix A

I. SAT Conclusions for P-16-0510 (shown below)

Per the SAT Report, the following determinations were made during the SAT Meeting.

- Physical form: Solid (neat); Imported as ~50% PMN material in common aqueous or alcohol solvent; Processing: Solution, ≤5% PMN material in fragrance formulation; End Use: Solution or solid, ≤0.25-2% in consumer products then destroyed (reacts with thiols and amines in odorous compounds)
- Absorption of the LMW (8% < 500, 32% < 1000) is expected to be good through the lungs, and poor through the skin and GI tract based on physical/chemical properties (estimated water solubility 1.085 g/L). If the PMN Is in solid form, then absorption is predicted to be nil-poor all routes.
- There is concern for mutagenicity, developmental toxicity, reproductive effects and neurotoxicity and a marginal concern for oncogenicity based on the acrylamide functional groups.
  Note: the acrylate analogs [dipropylene glycol diacrylate (DPGD) and 1,6-hexamethylene diacrylate (HDDA)] were not originally identified during SAT.

II. Analog Identification

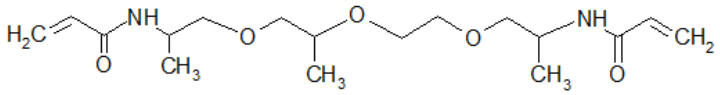
Risk MOE calculations for the LMW fractions were done using two PODs based on:

1. ECHA registration data submitted on dipropylene glycol diacrylate (DPGD) and its structural analog 1,6-hexamethylene diacrylate (HDDA) included in the ECHA registration[2], and
2. Acrylamide data evaluated in the EPA IRIS (2010) Toxicological Review of Acrylamide[3].

The structures of the PMN and of the analogs used to assess risk are shown below. DPGD/HDDA was selected as the most appropriate analog for quantitative risk assessment.

[2] ECHA (2011) *Oxybis(methyl-2,1-ethanediyl) diacrylate, EC number: 260-754-3, CAS number: 57472-68-1*, European Chemicals Agency (ECHA), available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14685/1

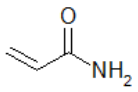
[3] EPA (2010) *Toxicological Review of Acrylamide (CAS No. 79-06-1), In Support of Summary Information on the Integrated Risk Information System (IRIS)*, EPA/635/R-07/009F, 459 pp., available at: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0286tr.pdf



P-16-0510 CASRN 1792208-65-1

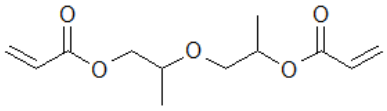
Analogs used to assess health risk

Analog for LMW Fraction of PMN

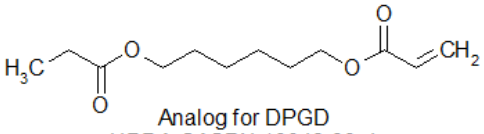


Acrylamide
CASRN 79-06-1

Analog for Entire PMN



DPGD CASRN 57472-68-1



Analog for DPGD
HDDA CASRN 13048-33-4

Both acrylamide and DPGD/HDDA may lead to adverse effects in biological systems *via* Michael Addition reactions; however, acrylamides have been shown to be less reactive than acrylates with cysteine residues such as DPGD/HDDA (*i.e.*, more than an order of magnitude slower).[4] Therefore, DPGD/HDDA was selected as the more appropriate analog for use with determining potential risks of concern for the PMN substance. Note, the data for acrylamide and DPGD/HDDA are provided for comparative purposes for the evaluation of points of departure (PODs), human equivalent doses/concentrations (HEDs/HECs), and risk evaluations. The PODs that served as the bases for the HEDs/HECs are provided in Table 1.

[4] Mather *et al*. (2006) *Michael Addition Reactions in Macromolecular Design for Emerging Technologies*, PROGRESS IN POLYMER SCIENCE, Vol. 31, pp. 487-531, at p. 523.

Table 1. Route-specific PODs and HEDs/HECs based on DPGD/HDDA and Acrylamide.

Chemical Substance	Study Type	Hazard Endpoint and Effect level(s)	Route-specific PODs		HED or HEC
DPGD/HDDA	OECD TG 422 (oral gavage)	Systemic toxicity, body weight, liver weight, clinical chemistry 250 mg/kg-bw/day (males/females)(NOAEL)[a]	Oral[b]	Gen. Pop.	59 mg/kg-bw/day
			Inhalation[c]	Workers	617 mg/m^3
				Gen. Pop. / Consumer	217 mg/m^3
			Dermal[d]	Workers / Consumer	552 mg/kg-bw/day
Acrylamide	Chronic drinking water	Neurotoxicity (nerve degeneration) 0.27 mg/kg-bw/day (male rats)($BMDL_{05}$)[e]	Oral[f]	Gen. Pop.	0.053 mg/kg-bw/day
			Inhalation[f]	Workers	0.424 mg/m^3
				Gen. Pop. / Consumer	0.212 mg/m^3
			Dermal[g]	Workers / Consumer	0.26 mg/kg bw/day

[a] ECHA (2011) *supra* note 2, at "Repeated dose toxicity: oral".
[b] EPA (2011) *Recommended Use of Body Weight3/4 as the Default Method in Derivation of the Oral Reference Dose*, EPA/100/R11/0001, 50 pp., at p. ix; the oral NOAEL of 250 mg/kg-bw/day was converted to an HED as follows: oral NOAEL × $(BW_{animal} \div BW_{human})^{1/4}$ = 250 mg/kg-bw/day × (0.25 kg ÷ 80 kg)$^{1/4}$ = 59 mg/kg-bw/day (assuming 100% absorption in rat and human).
[c] ECHA (2012) *Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.8: Characterisation of dose[concentration]-response for human health, version 2.1*, ECHA-2010-G-19-EN, 195 pp., at pp. 59 (workers) and 58 (general population); the oral NOAEL was converted to an inhalation value as follows: workers - Oral NOAEL (mg/kg-bw/day) ÷ 0.38 m^3/kg-bw (rat 8-hour respiratory rate) × (6.7 m^3 [human 8-hour respiratory rate] ÷ 10 m^3 [worker 8-hour respiratory rate] × 7 days [rat exposure duration] ÷ 5 days [worker exposure duration]; general population - Oral NOAEL (mg/kg-bw/day) ÷ 1.15 m^3/kg-bw (rat 24-hour respiratory rate)(assuming 100% absorption).
[d] *Id*. at p. 63; the oral NOAEL was converted to a dermal value as follows: oral NOAEL × [($ABS_{oral\text{-}rat}$; 100%) ÷ ($ABS_{derm\text{-}human}$; **15%**)] × $(BW_{animal} \div BW_{human})^{1/4}$, where $ABS_{oral\text{-}rat}$ = absorption of DPGD/HDDA by the oral route in the rat, $ABS_{derm\text{-}human}$ = absorption of DPGD/HDDA by the dermal route in humans.

[e] EPA (2010) *supra* note 1, at p. 204.
[f] *Id*. at pp. 205 (oral) and 220 (inhalation); note, EPA (2010) used 70 kg as the weight for an adult; the HEC was re-calculated for the assessment provided herein using 80 kg, as follows:
Worker $AirHEC_{BMDL}$ = $OralHED_{BMDL}$ × 80 kg × (day ÷ 10 m^3) = 0.053 mg/kg-bw/day × 80 kg × (day ÷ 10 m^3) = 0.424 mg/m^3, or
General Population $AirHEC_{BMDL}$ = $OralHED_{BMDL}$ × 80 kg × (day ÷ 20 m^3) = 0.053 mg/kg-bw/day × 80 kg × (day ÷ 20 m^3) = 0.212 mg/m^3.
[g] ECHA (2012) *Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.8: Characterisation of dose[concentration]-response for human health, version 2.1*, ECHA-2010-G-19-EN, 195 pp., at pp. 59 (workers); the oral $BMDL_{05}$ was converted to a dermal value as follows: oral BMDL × [($ABS_{oral\text{-}rat}$; 100%) ÷ ($ABS_{derm\text{-}human}$; **25%**)] × $(BW_{animal} \div BW_{human})^{1/4}$, where $ABS_{oral\text{-}rat}$ = $ABS_{derm\text{-}human}$ = absorption of acrylamide by the dermal route in humans.

III. Benchmark MOEs for General Population Risk via Ingestion

DPGD/HDDA

A benchmark MOE of 30 was used for determining whether potential non-cancer risks of concern may exist for oral exposures to the general population based on the DPGD/HDDA POD, determined as follows:

10 Uncertainty Factor (UF) for intra-species extrapolation (*i.e.*, human to human or UF_H) and 3 UF for interspecies extrapolation (*i.e.*, animal to human or UF_A). The default UF_A consists of a factor of 3.16 for toxicokinetics and 3.16 for toxicodynamics (*i.e.*, UFA = TK × TD = 10); however, the TK factor was reduced to 1 because allometric scaling was used to derive an HED. An MOE less than 30 was considered to represent potential non-cancer risks of concern, whereas an MOE greater than or equal to 30 was considered to represent an acceptable level of risk.

Acrylamide

A benchmark MOE of 30 was used for determining whether potential non-cancer risks of concern may exist for oral exposures to the general population based on the Acrylamide POD. The benchmark MOE is determined as follows:

10 UF for intra-species extrapolation (*i.e.*, human to human or UF_H) and 3 UF for interspecies extrapolation (*i.e.*, animal to human or UF_A). The default UF_A consists of a factor of 3.16 for toxicokinetics and 3.16 for toxicodynamics (*i.e.*, UFA = TK × TD = 10); however, the TK factor was reduced to 1 because physiologically-based pharmacokinetic modeling was used to derive an HED. An MOE less than 30 was considered to represent potential non-cancer risks of concern, whereas an MOE greater than or equal to 30 was considered to represent an acceptable level of risk.

IV. Calculated MOEs for General Population Risk via Drinking Water

Fish ingestion was estimated to be negligible because the PMN was not bioaccumulative. For the drinking water scenario (Table 2), the MOEs for the general population exceeded the acceptable benchmark MOEs of 30 indicating that **risks are not identified for general population for systemic toxicity and neurotoxicity via ingestion of drinking water based on analog data.**

Table 2: Oral exposure scenarios and MOEs based on DPGD/HDDA and acrylamide for the general population from drinking water

General Population MOE Calculations MOE = (POD x Abs Rate) / (ADR x Abs Rate x Component %) Benchmark (acceptable) MOE ≥30 or 100																										
Exposure Scenarios and Values[1]		**POD= N/LOAEL (mg/kg/ day)**		**POD Route Absorption Adj[2]**				**Exposure ADR (mg/kg/day)**		**Exposure Route Absorption Adj[2]**		**Multiplier for Sensitive Sub-populations[3]**		**Structural Alert/ Component as % of PMN[4]**				**Margin of Exposure (POD/PMN Dose)[5]**	**Benchmark MOE**
General Population MOE Calculations																										
DPGD/HDDA																										
Drinking Water	(	59	x	100%	)	÷	(	8.90E-05	x	100%	x	1.00	x	100%	)	=	662921	30								
Drinking Water	(	59	x	100%	)	÷	(	8.90E-05	x	100%	x	4.17	x	100%	)	=	158974	30								
Acrylamide																										
Drinking Water	(	0.053	x	100%	)	÷	(	8.90E-05	x	100%	x	1.00	x	32%	)	=	1861	30								
Drinking Water	(	0.053	x	100%	)	÷	(	8.90E-05	x	100%	x	4.17	x	32%	)	=	446	30								

[1] General Population Acute Dose Rates (ADR) are from the Exposure Report and are generated using E-FAST which assumes a 100% absorption rate, and uses an average adult body weight of 80 kg.

[2] Absorption adjustments for Focus: Assume 100% POD; if risks, consider adjusting for absorption, etc.

[3] Multiplier based on increased drinking water consumption for infants. Multiplier would be less for older populations, so this value is worst-case.

[4] Acrylamide exposure dose was adjusted to only apply to the low-molecular-weight fraction on the PMN. This adjustment is a conservative estimate in assuming that acrylamide represents the entire low-molecular-weight fraction of the PMN.

[5] Benchmark (Acceptable) MOEs are 100 for NOAEL-based assessment and 1000 for LOAEL-based assessment, unless modified based on other toxicokinetic adjustments.

V. Benchmark MOEs for Consumers Risk via Inhalation and Dermal Exposure

DPGD/HDDA

A benchmark MOE of 100 or 30 was used for determining whether potential non-cancer risks of concern may exist for inhalation and dermal exposures to the general population, respectively. The inhalation benchmark MOE of 100 consisted of an overall uncertainty factor that consisted of the following: 10 for intra-species extrapolation (*i.e.*, human to human or UF_H) and 10 for interspecies extrapolation (*i.e.*, animal to human or UF_A). The dermal benchmark MOE of 30 consisted of an overall uncertainty factor that consisted of the following: 10 for intra-species extrapolation (*i.e.*, human to human or UF_H) and 3 for interspecies extrapolation (*i.e.*, animal to human or UF_A). The default UF_A consists of a factor of 3.16 for toxicokinetics and 3.16 for toxicodynamics (*i.e.*, UFA = TK × TD = 10); however, the TK factor was reduced to 1 because allometric scaling was used to derive an HED. An MOE less than 100 was considered to represent potential non-cancer risks of concern, whereas an MOE greater than or equal to 100 was considered to represent an acceptable level of risk.

Acrylamide

A benchmark MOE of 30 and 100 was used for determining whether potential non-cancer risks of concern may exist for inhalation and dermal exposures to the general population, respectively. The inhalation benchmark MOE of 30 consisted of an overall uncertainty factor

that consisted of the following: 10 for intra-species extrapolation (*i.e.*, human to human or UF_H) and 3 for interspecies extrapolation (*i.e.*, animal to human or UF_A). The default UF_A consists of a factor of 3.16 for toxicokinetics and 3.16 for toxicodynamics (*i.e.*, UFA = TK × TD = 10); however, the TK factor was reduced to 1 because physiologically-based pharmacokinetic modeling was used to derive an HEC. The dermal benchmark MOE of 100 consisted of an overall uncertainty factor that consisted of the following: 10 for intra-species extrapolation (*i.e.*, human to human or UF_H) and 10 for interspecies extrapolation (*i.e.*, animal to human or UF_A). An MOE less than 30 (inhalation) or 100 (dermal) was considered to represent potential non-cancer risks of concern, whereas an MOE greater than or equal to 30 (inhalation) or 100 (dermal) was considered to represent an acceptable level of risk.

VI. Calculated MOEs for Consumer Risk via Inhalation/Dermal Exposures

For consumer inhalation exposures from the use of general purpose cleaners (Table 3), the MOEs exceeded the respective acceptable benchmark MOEs for acrylamide and DPGD/HDDA.

For dermal contact, the MOE was well above the benchmark MOE for the selected analog DPG/HDDA. The dermal MOE using acrylamide was slightly below or at the benchmark MOE. As noted previously, EPA considers DPGD/HDDA to be a better analog, therefore, RAD concludes that **risks were not identified for consumers for health effects via inhalation or dermal contact, based on analog data**.

Table 3: Inhalation and dermal exposure scenarios and MOEs based on DPGD/HDDA and acrylamide for consumers.

Consumer MOE Calculations
MOE = (POD x Abs Rate) / (ADR/Conc. x Abs Rate x Component %) Benchmark (acceptable) MOE ≥30 or 100

Exposure Scenarios and Values[1]		POD mg/kg-day / mg/m^3		POD Route Absorption Adj[2]			Exposure ADR (mg/kg/day) / Peak Conc. (mg/m^3)		Exposure Route Absorption Adj[2]		Multiplier for Sensitive Sub-populations		Structural Alert/ Component as % of PMN[4]			Margin of Exposure (POD/PMN Dose)	Benchmark MOE
CONSUMER RISK - General Purpose Cleaner																	
DPGD/HDDA																	
Dermal	(	552	x	100%	)	÷	(8.60E-03	x	100%	x	1.00	x	100%	)	=	64186	30
Inhalation	(	217	x	100%	)	÷	(4.00E-05	x	100%	x	1.00	x	100%	)	=	5425000	100
Acrylamide																	
Dermal	(	0.260	x	100%	)	÷	(8.60E-03	x	100%	x	1.00	x	32%	)	=	94	100
Inhalation	(	0.212	x	100%	)	÷	(4.00E-05	x	100%	x	1.00	x	32%	)	=	16563	30

[1] Consumer Acute Dose Rates (ADR) are from the Exposure Report and are generated using E-FAST which assumes a 100% absorption rate, and uses an average adult body weight of 80 kg. Consumer ADRs and Peak Concentrations are generated using the Consumer Exposure Module within the E-FAST CBI version called "NCEM2" model.

[2] Absorption adjustments for Focus: Assume 100% POD; if risks, consider adjusting for absorption, etc.

[3] Benchmark (Acceptable) MOEs are 100 for NOAEL-based assessment and 1000 for LOAEL-based assessment, unless modified based on other toxicokinetic adjustments.

[4] Acrylamide exposure dose was adjusted to only apply to the low-molecular-weight fraction on the PMN. This adjustment is a conservative estimate in assuming that acrylamide represents the entire low-molecular-weight fraction of the PMN.

VII. Benchmark MOEs for Worker Risk via Inhalation

DPGD/HDDA

A benchmark MOE of 100 was used for determining whether potential non-cancer risks of concern may exist for inhalation exposures to workers. This value consisted of an overall uncertainty factor that consisted of the following: 10 for intra-species extrapolation (*i.e.*, human to human or UF_H) and 10 for interspecies extrapolation (*i.e.*, animal to human or UF_A). An MOE less than 100 was considered to represent potential non-cancer risks of concern, whereas an MOE greater than or equal to 100 was considered to represent an acceptable level of risk.

Acrylamide

A benchmark MOE of 30 was used for determining whether potential non-cancer risks of concern may exist for inhalation exposures to workers. This value consisted of an overall uncertainty factor that consisted of the following: 10 for intra-species extrapolation (*i.e.*, human to human or UF_H) and 3 for interspecies extrapolation (*i.e.*, animal to human or UF_A). The default UF_A consists of a factor of 3.16 for toxicokinetics and 3.16 for toxicodynamics (*i.e.*, UFA = TK × TD = 10); however, the TK factor was reduced to 1 because physiologically-based pharmacokinetic modeling was used to derive an HEC. An MOE less than 30 was considered to represent potential non-cancer risks of concern, whereas an MOE greater than or equal to 30 was considered to represent an acceptable level of risk.

VIII. Calculated MOEs for Worker Risk via Inhalation

For inhalation scenarios using DPGD/HDDA and acrylamide (Table 4), the MOEs for workers exceeded the acceptable benchmarks of 100 and 30, respectively. Therefore, RAD concludes that **risks were not identified for workers for health effects via inhalation, based on analog data.**

Table 4: Inhalation exposure scenarios and MOEs based on DPGD/HDDA and acrylamide for workers

Worker Risks via Inhalation; HEC in mg/m^3 **MOE = (Adj HEC x Abs rate) / (Adj PDR x Abs rate x Component %); Benchmark (acceptable) MOE ≥30 or 100**								
Exposure Scenarios	HEC[1] (mg/m^3)	Potential Dose Rate[2] (mg/day)	Exposure Route Absorption Adj[3]	8 hour exposure concentration[4] (mg/m^3)	Exposure Route Absorption Adj[3]	Structural Alert/ Component as % of PMN[5]	Margin of Exposure (HEC/ PDR)	Inhalation Fold Factor (Benchmark/ MOE)[6]
WORKER RISK								
DPGD/HDDA								(100)
Inhalation	617	1.3E-02	100%	0.0013	100%	100%	474615	0.0
Acrylamide								(30)
Inhalation	0.424	1.3E-02	100%	0.0013	100%	32%	1019	0.1

[1] HEC is the Human Equivalent Concentration adjusted from the animal POD based on exposure duration.

[2] Inhalation doses in mg/day are from the Engineering Report generated using ChemSTEER. Unless otherwise stated, the assumption is an 8-hr day.

[3] Absorption adjustments for Focus: Assume 100% POD; if risks, consider adjusting for absorption, etc.

[4] PDR in mg/day is converted to an exposure concentration mg/m3 using this formula: mg/m3 = (mg/day) / (8 hrs/day x 1.25 m3/hr). The breathing rate used in the exposure assessment for humans is 1.25 m3/hour S

[5] Acrylamide exposure dose was adjusted to only apply to the low-molecular-weight fraction on the PMN. This adjustment is a conservative estimate in assuming that acrylamide represents the entire low-molecular-weight fraction of the PMN.

[6] Fold factor = value to be applied to bring INHALATION MOE up to acceptable level, used by the Industrial Hygienist to determine respirator recommendations. MOEs are 100 for NOAEL-based assessment and 1000 for LOAEL-based assessment, unless modified based on other toxicokinetic adjustments.

IX. Benchmark MOEs for Worker Risk via Dermal Exposure

DPGD/HDDA

A benchmark MOE of 30 was used for determining whether potential non-cancer risks of concern may exist for dermal exposures to workers. This value consisted of an overall uncertainty factor that consisted of the following: 10 for intra-species extrapolation (*i.e.*, human to human or UF_H) and 3 for interspecies extrapolation (*i.e.*, animal to human or UF_A). The default UF_A consists of a factor of 3.16 for toxicokinetics and 3.16 for toxicodynamics (*i.e.*, UFA = TK × TD = 10); however, the TK factor was reduced to 1 because allometric scaling was used to derive an HED. An MOE less than 30 was considered to represent potential non-cancer risks of concern, whereas an MOE greater than or equal to 30 was considered to represent an acceptable level of risk.

Acrylamide

A benchmark MOE of 100 was used for determining whether potential non-cancer risks of concern may exist for dermal exposures to workers. This value consisted of an overall uncertainty factor that consisted of the following: 10 for intra-species extrapolation (*i.e.*, human to human or UF_H) and 10 for interspecies extrapolation (*i.e.*, animal to human or UF_A). An MOE less than 100 was considered to represent potential non-cancer risks of concern, whereas an MOE greater than or equal to 100 was considered to represent an acceptable level of risk.

X. Calculated MOEs for Worker Risk via Dermal Exposures

For dermal scenarios using DPGD/HDDA (Table 5), the MOE for workers exceeded the acceptable benchmark of 30. For dermal scenarios using acrylamide (Table 5), the MOE for workers was below the benchmark of 100. As described previously, EPA considers DPGD/HDDA to be the more appropriate analog. Therefore, RAD concludes **that risks were not identified for workers for health effects via dermal contact, based on analog data.**

Table 5: Dermal exposure scenarios and MOEs based on acrylamide and DPGD/HDDA for workers

Worker Calculations MOE = (POD x Abs Rate) / ((PDR x Abs Rate) / BW) Acceptable MOE ≥30, 100																				
Exposure Scenarios and Values[1]		**POD (mg/kg/ day)**		**POD Route Absorption Adj[2]**			**Potential Dose Rate (mg/day)**		**Exposure Route Absorption Adj[2]**		**Structural Alert/ Component as % of PMN[3]**		**Avg BW[4] All Adults, 80 (kg)**			**Margin of Exposure[5] (POD/PMN Dose)**	**Benchmark MOE**
WORKER RISK																				
DPGD/HDDA																				
Dermal	(	552	x	100%	)	÷	(	1.1E+03	x	15%	x	100%	÷	80	)	=	267.6364	30
Acrylamide																				
Dermal	(	0.26	x	100%	)	÷	(	1.1E+03	x	15%	x	32%	÷	80	)	=	0.3939	100

[1] Unless otherwise stated, the assumption is an 8-hr day. The EPA/OPPT 2-Hands Dermal Contact with Liquids Model calculates worker dermal exposures to a liquid. Model assumptions are: (1) surface area of contact equals two hands (1,070 cm2); (2) high-end default value of quantity remaining on skin = 2.1 mg/cm2 (low-end default = 0.7 mg/cm2); (3) weight fraction of chemical in liquid; (4) 1 contact/worker-day; (5) no use of controls or gloves to reduce exposure; (6) exposure duration = 1 to 4 hours based expectation that worker will, at a minimum, thoroughly wash hands at lunch or end of the day.

[2] Absorption adjustments for Focus - Assume 100% for POD; For Exposure. If risks, consider adjustments for absorption,etc.

[3] Acrylamide exposure dose was adjusted to only apply to the low-molecular-weight fraction on the PMN. This adjustment is a conservative estimate in assuming that acrylamide represents the entire low-molecular-weight fraction of the PMN.

[4] USEPA 2011. Exposure factors handbook, final report, EPA/600-R09/052F, 2011, Chapter 8 Body Weight Studies,Table 8-1, Recommended Values for Body Weight http://www.epa.gov/ncea/efh/pdfs/efh-chapter08.pdf

[5] Benchmark (Acceptable) MOEs are 100 for NOAEL-based assessment and 1000 for LOAEL-based assessment, unless modified based on other toxicokinetic adjustments.

XI. Conclusions

Non-cancer risks

A quantitative evaluation of potential non-cancer risks of concern was performed on the PMN

substance using DPGD/HDDA and acrylamide. Though acrylamide was shown for comparative purposes, DPGD/HDDA was used for identifying potential non-cancer risks of concern. Based on read across evaluations using DPGD/HDDA, the PMN substance is not expected to pose non-cancer risks of concern to workers, the general public, or consumers.

Cancer risks

A quantitative evaluation of potential cancer risks of concern was not performed on the PMN substance because of the absence of chronic repeated dose/concentration data on the PMN substance nor on the analogs selected for risk evaluation herein (*i.e.*, DPGD/HDDA). Though acrylamide was initially identified for read across to the PMN substance and was shown in a comparative fashion to DPGD/HDDA for potential non-cancer risks, a quantitative evaluation of potential cancer risks of concern was not performed with acrylamide for several reasons. First, the feedstocks for the PMN substance include methyl oxirane polymer with oxirane bis(2-aminopropyl) ether, which is reacted with 2-propenoyl chloride to yield the PMN substance. Acrylamide would be a suitable analog for 2-propenoyl chloride; however, this component is quenched in the reaction with maximum residuals in the PMN substance below 0.001 weight percent (wt%).[5] In contrast, DPDG/HDDA is a suitable conservative analog for methyl oxirane polymer and oxirane bis(2-aminopropyl) ether, which constitute 83 wt% of the PMN substance with a maximum residual of 5 wt%, collectively.[6]

Given the low amount of 2-propenyoyl chloride in the PMN substance, EPA concluded that despite the absence of chronic repeated dose/concentration data on DPDG/HDDA, there was sufficient evidence to support a qualitative evaluation of the potential cancer risks of concern for the PMN substance using DPDG/HDDA, as discussed below.[7] First, the genotoxic potential of DPGD/HDDA was evaluated with *in vitro* assays (Ames with and without metabolic activation in TA98, TA100, TA1535, TA1537, and TA1538)[8] and an *in vivo* assay (*i.e.*, OECD TG 474 Mammalian Erythrocyte Micronucleus Test)[9]; the ECHA registrants of these data concluded that the results were negative for frameshift/base pair mutations and clastogenic/aneugenic effects, respectively. Second, DPGD/HDDA was evaluated in a combined repeated dose toxicity study with the reproduction/developmental toxicity screen by gavage at dose levels up to 750 mg/kg-bw/day. The ECHA registrants of these data identified a systemic NOAEL of 250 mg/kg-bw/day for male/female rats and a reproductive toxicity NOAEL of 750 mg/kg-bw/day, the highest dose tested.[10] Finally, the PMN substance was evaluated in a series of skin sensitization assays both *in vitro* and *in vivo*.[11] The PMN submitter concluded that the results from these studies were

[5] See PMN Form (*i.e.*, EPA Form 7710-25) for P-16-0510, at p. 5.
[6] *Id*.
[7] Note, the low predicted absorption potential of the LWF of PMN substance by the dermal and gastrointestinal routes of exposure provide additional qualitative support.
[8] ECHA (2011) *supra* note 2, at "Genetic toxicity: in vitro".
[9] *Id*. at "Genetic toxicity: in vivo".
[10] *Id*. at "Repeated dose toxicity: oral".
[11] Memorandum (May 3, 2017); From: [redacted]; To [redacted]; Through: [redacted]; RE: Review of Sensitization Data for the PMN substance, P-16-0510, Office of Chemical

negative; EPA concurred with these conclusions.[12] Of particular note, the PMN substance was evaluated using the Direct Peptide Reactivity Assay (DPRA) (OECD TG 442C). Though this study is not aimed at evaluating carcinogenic potential, it does provide useful information on the propensity of a chemical substance to covalently bind to both soft (*i.e.*, cysteine) and hard (*i.e.*, lysine) nucleophiles. Since purine and pyrimidine bases are considered hard electrophiles, the lack of reactivity between the PMN substance and the lysine residues in the DPRA provides suggestive evidence, with caveats[13], that the PMN substance would not react appreciable with DNA.[14] Therefore, EPA concluded that a qualitative evaluation of potential cancer risks of concern was sufficient to designate this hazard as a low priority and to determine that quantitative data represented a data gap, but they were not needed on this endpoint to determine the actual risk.

Safety and Pollution Prevention, United States Environmental Protection Agency, Washington, D.C., 20460, 6 pp.

[12] *Id*. at p. 2.

[13] For example, chemical substances that are auto-oxidized or metabolically activated to haptens may not test positive in this assay.

Calculation of Maximum % Without Risk

This worksheet presents the results of a calculation to estimate the maximum percentage of the PMN substance that can be used in a formulation without identified risks. The calculation sets up a ratios, based on themargin of exposure (MOE) calculated in the risk assessment (point of departure/exposure estimate), the benchmark MOE used to interpret risk, and the percent of the PMN substance in the formulation used. This calculation provides the theoretical "allowable percent" in a formulation that would yield an MOE that would not exceed the benchmark MOE. Since this calculation is mathematical, it is possible to obtain results that do not make sense, specifically the outcome could be greater than 100%. In this case, the outcome should be interpreted as no identified risks at 100%.

The equation used is as follows:

(MOE/Benchmark MOE) * Percent PMN in calculation = Theoretical Allowable Percent

Two analogs were used: DPDG/HDDA is considered the most appropriate analog. Acrylamide is included for comparison purposes.

Theoretical Allowable Percent

DPGD/HDDA

Scenario	MOE	Benchmark MOE	% in Formulation	MOE/BM	Theoretical Allowable % (% x Ratio)	Interpretation
Worker Inhal Proc 2	474,615	100	2	4746.2	9492.3	No Limit
Worker Dermal	263	30	50	8.8	438.3	No Limit
Consumer Inhal	5425000	100	2	54250	108500.0	No Limit
Consumer Dermal	64186	30	2	2139.5	4279.1	No Limit

The inhalation benchmark MOE of 100 consisted of an overall uncertainty factor that consisted of the following: 10 for intra-species extrapolation (i.e., human to human or UFH) and 10 for interspecies extrapolation (i.e., animal to human or UFA).

The dermal benchmark MOE of 30 consisted of an overall uncertainty factor that consisted of the following: 10 for intra-species extrapolation (i.e., human to human or UFH) and 3 for interspecies extrapolation (i.e., animal to human or UFA). The default UFA consists of a factor of 3.16 for toxicokinetics and 3.16 for toxicodynamics (i.e., UFA = TK × TD = 10); however, the TK factor was reduced to 1 because allometric scaling was used to derive an HED.

Under interpretation, "No Limit" means that based on hazards, the PMN substance can be used at concentrations up to 100% without identified risks (e.g., MOE < benchmark).

Theoretical Allowable Percent

Acrylamide

Scenario	MOE	Benchmark MOE	% in Formulation	MOE/BM	Theoretical Allowable % (% x Ratio)	Interpretation
Worker Inhal Proc 2	326	30	2	10.9	21.7	Upper Limit
Worker Dermal	0.12	100	50	0.001	0.1	Upper Limit
Consumer Inhal	5300	30	2	176.7	353.3	No Limit
Consumer Dermal	30.27	100	2	0.3027	0.6	Upper Limit

The inhalation benchmark MOE of 30 consisted of an overall uncertainty factor that consisted of the following: 10 for intra-species extrapolation (i.e., human to human or UFH) and 3 for interspecies extrapolation (i.e., animal to human or UFA). The default UFA consists of a factor of 3.16 for toxicokinetics and 3.16 for toxicodynamics (i.e., UFA = TK × TD = 10); however, the TK factor was reduced to 1 because physiologically-based pharmacokinetic modeling was used to derive an HEC.

The dermal benchmark MOE of 100 consisted of an overall uncertainty factor that consisted of the following: 10 for intra-species extrapolation (i.e., human to human or UFH) and 10 for interspecies extrapolation (i.e., animal to human or UFA).

Under interpretation, "No Limit" means that based on hazards, the PMN substance can be used at concentrations up to 100% without identified risks (e.g., MOE < benchmark).

The "Upper Limit" refers to the maximum concentration that can be used identified risks (e.g., MOE < benchmark).